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Commentary on Mandy & Lai

“Not just genes: Reclaiming a role for environmental influences on aetiology and outcome in autism”

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[Word count = 1,689]

Abstract

Mandy and Lai (2015) do the field a service in ‘reclaiming’ the role of pre- and post-natal environmental influences on the aetiology and course of autism spectrum conditions (ASC). This follows several decades where now discredited theories about putative psychogenic and biological disease models held sway, not least in the public mind. We discuss issues that arise from their review; including the need to identify how large the environmental influences on ASC are likely to be; the specificity of these environmental influences to ASC as opposed to a broader range of neurodevelopmental conditions and outcomes; how best to study complex interactions between genetic and environmental influences; and the promise of novel insights into their mechanisms of action. The review highlights current research that aims to better our understanding of the role of environmental factors in the aetiology and course of ASC and, in the near future, may offer the potential for personalised medicine approaches to intervention based on these discoveries.

[Word count = 160]

Keywords: autism spectrum conditions, autism spectrum disorders, genetics, environment, aetiology, neurodevelopment

Mandy and Lai (2015) provide a state-of-the-art summary of current knowledge of environmental influences on the emergence and course of autism spectrum conditions (ASC). This is important for several reasons; most notably because over several decades unfounded and now discredited theories about the role of the environment in ASC held sway, both over public perceptions and also in some arenas of clinical science and practice. These theories have ranged from the psychogenic notion put forward by Bettelheim of ‘refrigerator mothers’; to biological disease models such as the causal association with measles, mumps and rubella (MMR) vaccines proposed by Wakefield. Mandy and Lai (2015) summarise the evidence that now discounts these particular theories but the ripples that followed the promulgation of such ideas have had a long effect both on public and media perceptions and on what kind of science is undertaken in the field. By this we mean that for periods of time psychologists shied away from examining the role of family and parenting environmental influences on the developmental course of ASC. At the same time, suspicion was sometimes cast on those researching putative biological environmental factors in case they were going to ‘do another Wakefield’, in particular when this might change public health behaviour for the worse, as was the case for MMR. This timely and extensive review thus provides a potential springboard for research on the role of environmental factors in ASC. In our commentary, we highlight four key questions that arise out of the literature reviewed.

How big is the environmental influence on ASC?

Quantification of the magnitude of environmental influence on ASC relies on heritability estimates computed traditionally using twin studies. The early estimates for the genetic component were considerably higher (e.g., ~90% by Folstein & Rutter, 1977) than more recent ones (e.g., ~50% by Hallmayer et al., 2011). The reason for such a trend of

decreasing heritability estimates might lie in the choice of instrument for defining the phenotype, as discussed by the authors. Another potential explanation for this trend could be the increasingly better identification of neurogenic conditions commonly associated with ASC (e.g. Fragile X, Tuberous Sclerosis), which tend to be excluded from recent twin studies of ASC (Hallmayer et al., 2011). Stratifying by severity of symptoms leads to varying estimates of the additive genetic (and consequently, environmental and interaction) component in ASC; pointing to a larger impact of genetic factors in the extreme end of the autistic spectrum (Frazier et al., 2014). This trend is suggestive of an increase of phenocopies in the broader spectrum, i.e. similar phenotypes arising out of distinct genetic and environmental determinants. It is also worth noting that heritability estimates from twin-based studies differ considerably from those using recent genomewide methods (SNP-based heritability estimates) due to the former including potential non-additive genetic effects (Viding et al., 2013). Finally, aspects of ASC-related behaviour (e.g. theory of mind) show widely different estimates of the genetic and environmental components depending on the age at which the phenotype is measured (Hughes et al., 2005). In sum, the magnitude of the environmental influence on ASC is likely to depend on a) the choice of the phenotypic instrument, b) inclusion/ exclusion criteria based on severity of symptoms, as well as existing neurogenic conditions (for syndromic forms of ASC), c) choice of study design (SNP-based or twin-based), and potentially d) the age of the sample.

How important is the specificity of the risk factors for ASC?

One theme mentioned only briefly in the review, due to its focus on ASC, is the extent to which many of the environmental influences are also likely to play a role in the emergence and developmental course of a wide range of neurodevelopmental conditions. For

example, increased paternal age has been shown to be associated with a wide range of neurodevelopmental disorders in addition to ASC, including attention deficit hyperactivity disorder (ADHD), bipolar disorder and psychosis (D'Onofrio et al., 2014). The effect is at least in part likely due to increased rates of sporadic genetic mutations during spermatogenesis with advancing age. Similarly, traffic related air pollution has also been associated with higher levels of ADHD and conduct problems in mid-childhood (Newman et al., 2013).

It is now well established that co-occurrence of neurodevelopmental disorders is the norm and not the exception. For example, in childhood, intellectual disability, ADHD and anxiety are common in children with ASC. What is required in order to elucidate the role of environmental factors, and gene-environment interactions and correlations, in the aetiology of ASC but also more broadly in neurodevelopmental disorders, is to understand the common systems that are disrupted in this range of conditions and what common and distinct mechanisms affect these from early in prenatal neurodevelopment. Single gene disorders (e.g., fragile X syndrome, tuberous sclerosis) and copy number variants (CNVs) (e.g., 22q11.2 and 16p11.2) that are strongly associated with ASC act on synaptic development, plasticity and signalling and represent one 'common pathway' through which perturbations to developing brain systems can lead to ASC and other neurodevelopmental disorders (Moreno-De-Luca et al., 2013). Understanding how the environmental factors involved in the development of ASC may also impact on similar, or distinct, neural development and pathways will help tease apart how common and rare genetic and environmental factors might work, as well as identify potential treatment targets.

The recently suggested Research Domain Criteria (RDoC) framework provides a useful lens to view the evidence presented. A question that arises from this perspective is the utility of focussing on the *specificity* of the risk factors for ASC. An alternative way to

conceptualise risk factors might be based on the separate dimensions associated with extreme values in individuals with ASC (e.g., social-communicative behaviour, repetitive behaviour). Instead of asking whether an environmental factor increases the risk for ASC specifically, this alternative approach would address the impact of the risk factor separately on social-communicative behaviour and repetitive behaviour, and the developing neural and cognitive systems that underlie such behaviour. Focussing on such separable dimensions can arguably lead to two potentially useful outcomes. First, it can lead to aetiological insights that span across traditional psychiatric diagnostic categories. Second, it can help move toward individualised interventions by addressing specific environmental factors for individuals with deficits in a given dimension, irrespective of their specific diagnostic category. The challenge with this alternative approach is that of developing robust assays that capture the population-level variability in the separate dimensions of interest, as well as population-level variation in the susceptibility to various environmental risk factors.

How best to study gene environment interactions and correlations?

The role of gene-environment interactions and correlations in the aetiology and course of ASC will only be uncovered when studies are able to adopt a multi-generational approach. A recent study has reported intriguing new findings indicating not only a role for increasing paternal and maternal age for increasing risk of their offspring having an ASC but also increased risks in younger mothers (< 20 years) and when there is a wider discrepancy between parental ages (Sandin et al., 2015). The authors discuss possible mechanisms for these findings and they include possible gene-environment interaction and correlational effects in that for both men and women traits such as shyness and aloofness, that are seen at increased rates in family members of individuals with ASC compared to the general

population – where they are referred to as the ‘broader autism phenotype’ (BAP) – may affect when a person establishes an intimate relationship and has children, confounding the association between parental age and risk of ASC that goes beyond a simple environmental ‘ageing’ explanation. Further illustrating GxE interactions, the authors discuss the promising work on MET gene variability and susceptibility to traffic pollution (TRAP) (Volk et al., 2014). Earlier work by Persico and others have demonstrated a similar GxE interaction in Paraoxonase (*PON1*) genetic variability and exposure to organophosphates in increasing risk for ASC (D’Amello et al., 2005). Future studies should build on these pioneering studies in systematically examining the impact of the environmental risk factors on common and rare variations on the full set of ASC-related genes (SFARI Base <http://sfari.org/resources/sfari-base>; Autworks <http://autworks.hms.harvard.edu/>).

What insights do environmental factors provide on the underlying mechanisms for the development of ASC?

Early neurodevelopment is a candidate process believed to be associated with atypicalities in ASC. Environmental contributions to such atypicalities may operate through epigenetic mechanisms, as discussed by the authors (e.g. impact of prenatal valproate exposure on methylation profile of the Wnt signalling pathway, as well as a putative mechanism to explain the maternal age effect). However, the tissue or gene specificity of these epigenetic influences remains less well known, i.e. are these effects restricted to brain-expressed genes, and/or if such effects are maximal in a subset of brain-expressed genes that have been previously linked to ASC? If these effects are observed in tissues other than the brain, then studying the gene methylation profiles in such tissues (which are often easier to collect/measure) could be an informative direction for future research.

At a cellular level, the authors mention the role of microglial activation as a mechanism through which the immune system can influence early neurodevelopment. Prenatal sex hormones influence microglial activation, thus providing a potential mechanism through which hormonal effects are manifested in a developing brain (Baron-Cohen et al., 2015). Microglia deserve a special mention in the discussion of mechanisms for early neurodevelopment. In addition to being a key player of the immune system in the brain (in response to injury, pathology, or infection), microglia play a central role in the pruning of synapses (Salter & Beggs, 2014). Atypical synaptic pruning is a putative mechanism for atypical neurodevelopment seen in ASC (Thomas et al., in press). It would therefore be of interest to examine if and how the range of other environmental factors reviewed by the authors, can influence microglial activation.

Conclusion

In conclusion, Mandy and Lai provide a comprehensive walk through of current research that aims to better our understanding of the role of environmental factors in the aetiology and course of ASC. This review opens up fundamental questions for future research, which, in the near future, may offer the potential for personalised medicine approaches to intervention based on these discoveries.

References

(Highlighted references are in the target paper so should be removed from this list?)

- Baron-Cohen, S., Auyeung, B., Nørgaard-Pedersen, B., Hougaard, D. M., Abdallah, M. W., Melgaard, L.,...& Lombardo, M. V. (2015). Elevated fetal steroidogenic activity in autism. *Molecular Psychiatry*, 20, 369-376. doi: 10.1038/mp.2014.48.
- D'Amelio, M., Ricci, I., Sacco, R., Liu, X., D'Agruma, L., Muscarella, L. A.,...Persico, A. M. (2005). Paraoxonase gene variants are associated with autism in North America, but not in Italy: possible regional specificity in gene-environment interactions. *Molecular Psychiatry*, 10, 1006-1016.
- D'Onofrio, B. M., Rickert, M. E., Frans, E., Kuja-Halkola, R., Almqvist, C., Sjölander, A.,...Lichtenstein P. (2014). Paternal age at childbearing and offspring psychiatric and academic morbidity. *JAMA Psychiatry*, 71, 432-438. doi: 10.1001/jamapsychiatry.2013.4525.
- Folstein, S., & Rutter, M. (1977). Infantile autism: a genetic study of 21 twin pairs. *Journal of Child Psychology and Psychiatry*, 18, 297-321.
- Frazier, T. W., Thompson, L., Youngstrom, E. A., Law, P., Hardan, A. Y., Eng, C., & Morris, N. (2014). A twin study of heritable and shared environmental contributions to autism. *Journal of Autism and Developmental Disorders*, 44, 2013-2025. doi: 10.1007/s10803-014-2081-2.
- Hallmayer, J., Cleveland, S., Torres, A., Phillips, J., Cohen, B., Torigoe, T.,...Risch, N. (2011). Genetic heritability and shared environmental factors among twin pairs with autism. *Archives of General Psychiatry*, 68, 1095-1102. doi: 10.1001/archgenpsychiatry.2011.76
- Hughes, C., Jaffee, S. R., Happé, F., Taylor, A., Caspi, A., & Moffitt, T. E. (2005).

Origins of individual differences in theory of mind: from nature to nurture?

Child Development, 76, 356-370.

Mandy, W., & Lai, M.C. (2015) The role of the environment in the developmental psychopathology of autism spectrum conditions. *Journal of Child Psychology and Psychiatry*, in press.

Moreno-De-Luca, A., Myers, S. M., Challman, T. D., Moreno-De-Luca, D., Evans, D. W., & Ledbetter, D. H. (2013). Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence. *Lancet Neurology*, 12, 406-414. doi: 10.1016/S1474-4422(13)70011-5

Newman, N. C, Ryan, P., Lemasters, G., Levin, L., Bernstein, D., Hershey, G. K.,... Dietrich, K. N. (2013). Traffic-related air pollution exposure in the first year of life and behavioral scores at 7 years of age. *Environmental Health Perspectives*, 121, 731-736. doi: 10.1289/ehp.1205555

Salter, M. W., & Beggs, S. (2014). Sublime microglia: expanding roles for the guardians of the CNS. *Cell*, 158(1), 15-24.

Sandin, S., Schendel, D., Magnusson, P., Hultman, C., Surén, P., Susser, E.,... Reichenberg, A. (2015). Autism risk associated with parental age and with increasing difference in age between the parents. *Molecular Psychiatry*. doi: 10.1038/mp.2015.70

Thomas, M. S.C., Davis, R., Karmiloff-Smith, A., Knowland, V. C. P., & Charman, T. (in press). The over-pruning hypothesis of autism. *Developmental Science*. doi: 10.1111/desc.12303

Viding, E., Price, T. S., Jaffee, S. R., Trzaskowski, M., Davis, O. S., Meaburn, E. L.,...Plomin, R. (2013). Genetics of callous-unemotional behavior in children. *PLoS One*, 8, e65789. doi: 10.1371/journal.pone.0065789.

Volk, H. E., Kerin, T., Lurmann, F., Hertz-Picciotto, I., McConnell, R., & Campbell, D. B. (2014). Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. *Epidemiology*, 25, 44-47. doi: 10.1097/EDE.0000000000000030.